

1-28, 31, 33-35, 37-52

10/537,088

371, au priority-

PO = 12/02/02

2002 12 02

### AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

### LISTING OF CLAIMS:

I

1. (Original) An isolated, synthetic or recombinant  $\chi$ -conotoxin peptide having the ability to inhibit neuronal amine transporter comprising the following sequence of amino acids:

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys; or a sequence in which Gly, Tyr, Lys or Leu are subject to conservative amino acid substitution or side chain modification; with the proviso that the peptide is not  $\chi$ -MrIA,  $\chi$ -MrIB, Mar2, CMrVIA, Bnl.5, Mrl.3 or Aul.4; or a salt, ester, amide, prodrug or cyclised derivative thereof.

2. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide according to claim 1 ~~having the ability to inhibit neuronal amine transporter~~ comprising the following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 4

where

Xaa1 is selected from Trp, DTrp, Tyr, Phe, hPhe, Ala, MeY, Arg, Ben, Nap, Orn, pGlu,

DpGlu and a deletion;

Xaa2 is selected from Arg, Ala, Asn, Lys, Phe, BHK, Orn, Lys, DArg, Nle, DLys,

DMK, DAsn, Thr, ABZ, Nap, Cit, Val, Tyr, Trp, pGlu, DpGlu or a deletion;

pick 1 aa  
X1  
X2  
X3  
X4  
D+L forms will be examined together  
election in 2 applied to 3, 4, 7, 8, 9, 11, 15-22, 28, 42, 44, 46, 48, 50-52

10/450, 629

clp

3

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle, Ser or Phe;

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala, Asn, Trp, Phe and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;  
or a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to  
conservative amino acid substitution or side chain modification;

~~with the proviso that the peptide is not  $\chi$ -MrIA,  $\chi$ -MrIB, Mar2, Mr1.3 or Aul.4;~~

and or a salt, ester, amide, prodrug or cyclised derivative thereof.

3. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide  
according to claim 2 ~~having the ability to inhibit neuronal amino transporter~~ comprising the  
following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 4

where Xaa1 is selected from Trp, Tyr, Phe, hPhe, Ala, MeY, Arg, Ben and Nap,

Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK,

DAsn, Thr, ABZ, Nap, Cit and Val,

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys;  
or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to  
conservative amino acid substitution or side chain modification,  
or a salt, ester, amide, prodrug or cyclised derivative thereof.

4. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide according to claim 3 ~~having the ability to inhibit neuronal amino transporter~~ consisting of the following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 4

where Xaa1 is selected from Trp, Tyr, Phe, hPhe, Ala, MeY, Arg, Ben and Nap,

Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK,

DAsn, Thr, ABZ, Nap, Cit and Val,

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys, or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid substitution or side chain modification or a salt, ester, amide or prodrug thereof.

II  
5. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide according to claim 1 comprising the following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 5

pick 1  
X1-X9  
electron  
applied to d. 6,  
12-14, 23,  
28-41,  
43, 45, 47, 49  
where Xaa1 is an N-terminal residue and is selected from pGlu, DpGlu, Pro, Hyp or an N-acetylated amino acid residue;

Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK,

DAsn, Thr, ABZ, Nap, Cit, Val and a deletion,

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from <sup>C</sup>Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys; or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino substitution or sidechain modification, or a salt, ester, amide or prodrug thereof.

6. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide according to claim 5 consisting of the following sequence of amino acids:

Xaa1 Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 5

where Xaa1 is an N-terminal residue and is selected from pGlu, Pro, Hyp or an N-acetylated amino acid residue;

Xaa2 is selected from Arg, Asn, Lys, BHK, Orn, Lys, DArg, Nle, DLys, DMK, DAsn, Thr, ABZ, Nap, Cit, pGlu, Val and a deletion,

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys; or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino and substitution or said chain modification, or a salt or prodrug thereof.

7. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide according to claim 2 ~~having the ability to inhibit neuronal amine transporter~~ comprising the following sequence of amino acids:

Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys SEQ ID NO. 6

where Xaa2 is BHK, Orn, Arg, DArg or DMK;

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser,

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu, and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys; or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid or side chain modification, or a salt, ester, amide, prodrug or cyclised derivative thereof.

8. (Currently amended) ~~An isolated, synthetic or recombinant~~ The  $\chi$ -conotoxin peptide according to claim 7 having the ability to inhibit neuronal amine transporter consisting of the following sequence of amino acids:

Xaa2 Xaa3 Xaa4 Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 6

where Xaa2 is BHK, Orn, Arg, DArg or DMK;

Xaa3 is selected from Gly, Asp, Lys, Arg, Ala, Nle and Ser;

Xaa4 is selected from Val, Leu, Nle, Ile, Thr, Ala and Abu; and

Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys; or such a sequence where one or more of the loop 1 residues Gly, Tyr, Lys and Leu are subject to conservative amino acid or side chain modification, or a salt, ester, amide, prodrug or cyclised derivative thereof.

9. (Currently amended) ~~The peptide of any one of claims 2 to 4~~ according to claim 2 wherein Xaa1 is Trp, Tyr or hPhe.

10. (Currently amended) The peptide ~~of~~according to claim 9 wherein Xaa1 is Trp.

11. (Currently amended) The peptide ~~of any one of claims 2 to 4, 9 or 10~~ according to claim 2 wherein Xaa2 is Arg, Lys or Asn.

12. (Currently amended) The peptide ~~of~~according to claim 5 or 6 wherein Xaa1 is pGlu or DpGlu.

13. (Currently amended) The peptide ~~of any one of claims 5, 6 or 12~~ according to claim 5 wherein Xaa2 is a deletion.

14. (Currently amended) The peptide ~~of~~according to claim 5 or 6 wherein Xaa2 is BHK or Orn.

15. (Currently amended) The peptide ~~of any one of claims 2 to 14~~ according to claim 2 wherein Xaa3 is Gly or Asp.

16. (Currently amended) The peptide ~~of~~according to claim 15 wherein Xaa3 is Gly.

17. (Currently amended) The peptide ~~of any one of claims 2 to 16~~ according to claim 2 wherein Xaa4 is Leu, Nle or Val.

18. (Currently amended) The peptide of ~~any one of claims 2 to 17~~ according to claim 2 wherein Xaa5 is selected from the group consisting of His, Arg, Trp, Nal, Glu and a deletion.

19. (Currently amended) The peptide of ~~according to claim 18~~ wherein Xaa5 is Arg or His.

20. (Currently amended) The peptide of ~~any one of claims 2 to 19~~ according to claim 2 wherein Xaa6 is selected from the group consisting of Hyp, Pro, Ala, Tic, Pip, MeY, DMD, Phe, THZ, Glu, Nle, Tyr and a deletion.

21. (Currently amended) The peptide of ~~according to claim 20~~ wherein Xaa6 is Hyp or Pro.

22. (Currently amended) The peptide of ~~any one of claims 1 to 21~~ according to claim 1 wherein the Tyr of loop 1 has been replaced with MeY and/or the Leu of loop 1 is replaced with Hle or Nle.

?  
II (23. (Currently amended) The peptide of ~~any one of claims 1 to 22~~ according to claim 5 wherein the Tyr of loop 1 has been replaced with MeY and/or the Leu of loop 1 is replaced with Hle or Nle.

I 24. (Currently amended) The peptide of ~~any one of claims 1 to 23~~ according to claim 1 having from 11 to 20 amino acids.

3 - 155

II

25. (Original) An isolated, synthetic or recombinant  $\chi$ -conotoxin peptide as set forth in Table 2.

Groups

seq id nos: 13 - 165

~~15-165~~

26. (Original) An isolated, synthetic or recombinant peptide as set forth in Table 3, excluding

~~166-205~~

SEQ ID NO.1 and 7.

seq id nos. 166 - 215

156-205

I

27. (Currently amended) The peptide ~~of any one of claims 1 to 26~~ according to claim 1 with the ability to selectively inhibit neuronal noradrenaline transporter, and has negligible or no substantial anticholinergic effect.

I

28. (Original) A composition comprising an isolated, synthetic or recombinant  $\chi$ -conotoxin peptide having the ability to inhibit neuronal noradrenaline transporter, wherein said  $\chi$ -conotoxin peptide comprises the following sequence of amino acids:

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys, or such a sequence in which loop I residues Gly, Tyr, Lys or Leu are subject to conservative amino acid substitution or side chain modification, with the proviso that the peptide is not  $\chi$ -MrIA or  $\chi$ -MrIB; or a salt, ester, amide, prodrug or cyclised derivative thereof, and a pharmaceutically acceptable carrier or diluent.

29-30. (Cancelled)



278  
206  
31. (Original) Use of an isolated, synthetic or recombinant  $\chi$ -conotoxin peptide having the ability to inhibit neuronal noradrenaline transporter, wherein said  $\chi$ -conotoxin peptide comprises the following sequence of amino acids:

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQ ID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys, or such a sequence in which loop 1 residues Gly, Tyr, Lys or Leu are subject to conservative amino acid substitution or side chain modification, with the proviso that the peptide is not  $\chi$ -MrIA or  $\chi$ -MrIB; or a salt, ester, amide, prodrug or cyclised derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of urinary or cardiovascular conditions or diseases, or mood disorders, or for the treatment or control of pain or inflammation.

32. (Cancelled)

207  
209  
33. (Currently amended) Use of the ~~peptides of any one of claims 1 to 27~~ peptide according to claim 1 or compositions of any one of claims 28 to 30 as inhibitors as an inhibitor of neuronal noradrenaline transporter, or in the treatment or prophylaxis of diseases or conditions in relation to which the inhibition of neuronal noradrenaline transporter is associated with effective treatment.

207  
219  
34. (Currently amended) The use ~~as defined in~~ according to claim 33 in the treatment or prophylaxis of urinary or cardiovascular conditions or diseases or mood disorders or for the treatment or control of pain or inflammation.

207  
2+9

35. (Original) A method for the treatment or prophylaxis of urinary or cardiovascular conditions or diseases or mood disorders or for the treatment or control of pain or inflammation including the step of administering to a mammal an effective amount of an isolated, synthetic or recombinant  $\chi$ -conotoxin peptide having the ability to inhibit neuronal noradrenaline transporter, wherein said  $\chi$ -conotoxin peptide comprises the following sequence of amino acids:

Cys Cys Gly Tyr Lys Leu Cys Xaa5 Xaa6 Cys

SEQID NO. 3

where Xaa5 and Xaa6 are independently absent or represent any amino acid residue except Cys, or such a sequence in which Gly, Tyr, Lys or Leu are subject to conservative amino acid substitution or side chain modification, with the proviso that the peptide is not  $\chi$ -MrIA or  $\chi$ -MrIB; or a salt, ester, amide, prodrug or cyclised derivative thereof.

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36. (Cancelled)

37. (Currently amended) The method ~~of~~ according to claim 35 ~~or 36~~ wherein the peptide is administered substantially simultaneously or sequentially with other active agents useful in the treatment of the conditions, diseases or disorders.

II 38. (New) The peptide according to claim 6, wherein Xaa1 is pGlu or DpGlu.

39. (New) The peptide according to claim 5, wherein Xaa3 is Gly or Asp.

40. (New) The peptide according to claim 39, wherein Xaa3 is Gly.

II 41. (New) The peptide according to claim 5, wherein Xaa4 is Leu, Nle or Val.

I 42. (New) The peptide according to claim 7, wherein Xaa4 is Leu, Nle or Val.

II 43. (New) The peptide according to claim 5, wherein Xaa5 is selected from His, Arg, Trp, Nal, Glu and a deletion.

I 44. (New) The peptide according to claim 7, wherein Xaa5 is selected from His, Arg, Trp, Nal, Glu and a deletion.

II 45. (New) The peptide according to claim 5, wherein Xaa5 is Arg or His.

I 46. (New) The peptide according to claim 7, wherein Xaa5 is Arg or His.

II 47. (New) The peptide according to claim 5, wherein Xaa6 is selected from Hyp, Pro, Ala, Tic, Pip, MeY, DMD, Phe, THZ, Glu, Nle, Tyr and a deletion.

I 48. (New) The peptide according to claim 7, wherein Xaa6 is selected from Hyp, Pro, Ala, Tic, Pip, MeY, DMD, Phd, THZ, Glu, Nle, Tyr and a deletion.

II 49. (New) The peptide according to claim 47, wherein Xaa6 is Hyp or Pro.

I 50. (New) The peptide according to claim 48, wherein Xaa6 is Hyp or Pro.

I 51. (New) The peptide according to claim 2, wherein the Tyr of loop 1 has been replaced with MeY and/or the Leu of loop 1 is replaced with Hle or Nle.

I 52. (New) The peptide according to claim 7, wherein the Tyr of loop 1 has been replaced with MeY and/or the Leu of loop 1 is replaced with Hle or Nle.